Gadolinium-based nanoparticles for lung tumor investigations

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Lung cancer is the most common and most fatal cancer worldwide. Thus, improving early diagnosis and therapy is necessary. We have developed ultra-small gadolinium-based nanoparticles (USRPs) usable as multimodal contrast agent (MRI, SPECT, Fluorescence and X-ray tomography), and for therapeutic applications as radiosensitizing agent. These particles accumulate passively in tumors by EPR effect, and also permit an active targeting when functionalized with specific ligands, such as the cRGD motives. On the other hand, the lung is a unique organ because they can be targeted *via* the intravenous or *via* the airways.
We have developed an orthotopic model of lung tumor in *nude* mice, with H358 cells modified to stably express the luciferase gene. This modification allows the monitoring of tumor growth *in vivo* by bioluminescence imaging. We have studied the biodistribution of nanoparticles and tumor targeting *in vivo* by fluorescence imaging, X-ray tomography and Ultra-short echo-time MRI after intravenous or intrapulmonary administration. After intrapulmonary administration, the nanoparticles quickly passed from the lungs into the bloodstream and were distributed throughout the body (lung elimination half-life » 2h), before a renal elimination. Then, the particles allowed the passive targeting of orthotopic lung tumors, with good co-localization between the tumors (bioluminescence) and the nanoparticles (fluorescence and UTE-MRI), regardless of the route of administration. Moreover, the deposition of the nanoparticles around the tumor nodules was sufficient to generate a radiosensitizing effect when the mice were subjected to a single dose of 10 Gy conventional irradiation (mean survival time of 112 days versus 77 days for irradiated mice without USRPs treatment). At last, no apparent systemic toxicity or induction of inflammation was observed after intrapulmonary administration of the USRPs.
In conclusion, the direct administration of nanoparticles into the airways significantly increased their pulmonary delivery and the uptake by the tumors, allowing improved detection using non invasive imaging and therapy due to their radiosensitizing properties. The next step toward personalized therapy is the use if these nanoparticles for image-guided therapy.